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Lixivaptan: a vasopressin receptor antagonist for the treatment of hyponatremia

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Hyponatremia, the most common electrolyte disorder encountered in clinical practice, is associated with significant morbidity and mortality. The introduction of medications that specifically antagonize the vasopressin V2 receptor (vaptans) has provided a safe and effective means of therapy. Lixivaptan is the newest of these agents that reliably increase serum sodium levels in patients with euvolemic hyponatremia. However, significant questions remain regarding the specific indications for vaptans, and their potential impact on morbidity and mortality associated with hyponatremia.

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Hyponatremia is the most common electrolyte disorder encountered in clinical practice, and recent data have demonstrated that it is associated with an increase in mortality and morbidity even in patients in whom overt clinical symptoms may not be demonstrable.[1–3] Typically, the evaluation of patients with hyponatremia relies on assessment of volume status and classifies patients into hypovolemic, euvolemic, and hypervolemic states. This classification schema allows for determination of the underlying cause as well as aiding the clinician in making decisions on appropriate therapy. The most common forms of hyponatremia encountered in clinical practice are hypervolemic (due to congestive heart failure or cirrhosis) and euvolemic (largely due to the syndrome of inappropriate antidiuretic hormone action). Traditional therapies for hyponatremia have been limited, suboptimal, unreliable, and potentially toxic (Table 1). However, in 2005 the first drug that specifically antagonizes arginine vasopressin action at the receptor level was approved (the intravenous drug conivaptan, which antagonizes both the vasopressin V1a and V2 receptors) (Figure 1). In 2009, an oral vasopressin V2 receptor antagonist, tolvaptan, was also approved for the treatment of euvolemic and hypervolemic hyponatremia. Both of these agents (broadly termed 'vaptans') had clinical trial data demonstrating their efficacy in increasing serum sodium levels as well as increasing the percentage of patients with hyponatremia who normalized their serum sodium levels as compared with placebo.[4,5] Data also demonstrate the long-term safety and efficacy (out to approximately 2 years) of tolvaptan.[6] The ability to specifically target arginine vasopressin provided a physiologically based therapy for hyponatremia that was safe and reliable.

In two articles in this issue of *Kidney International*, Abraham and colleagues report on the effects of a new oral, non-peptide vasopressin V2 receptor, lixivaptan, in the treatment of both in- and outpatients with euvolemic hyponatremia.[7,8] The studies, LIBRA and HARMONY, differ in that the former trial required initial titration of lixivaptan in the inpatient setting, whereas, in the latter trial, lixivaptan was initiated in the outpatient setting (Table 2 summarizes the key characteristics and outcomes of both trials). Both studies are randomized, multinational, double-blinded placebo-controlled phase 3 trials. In both studies, the dosage of lixivaptan was titrated on the basis of daily serum sodium measurements. In both trials, patients randomized to lixivaptan showed greater rises in serum sodium values at day 7 after initiation of therapy, and were more likely to normalize their serum sodium, than those given placebo. Cessation of lixivaptan in both trials led to worsening of hyponatremia, suggesting that chronic therapy may be required in some patients.

Unique to the HARMONY study was the avoidance of in-hospital drug initiation and titration, which is currently recommended with tolvaptan. Using an outpatient strategy of starting patients on the lowest possible dose of lixivaptan (25 mg) with point-of-care testing of the serum sodium at 8 hours post-dose, the investigators demonstrated that only three patients in the lixivaptan group (and one in the placebo group) exceeded the desired sodium correction rates in the first 24 h; no subjects experienced an increase in serum sodium greater than 18 mmol/l within either a 48- or a 72-hour period; and no subjects had symptoms of osmotic demyelination syndrome. The ability to initiate therapy for hyponatremia in the outpatient setting is advantageous but

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Table 1 | Available therapies for hyponatremia

Therapy	Benefits	Drawbacks
Fluid restriction	Simple, easily implemented Minimal cost Can be useful in patients with urine osmolality $<$400-600 mosmol/kg	Minimally effective and requires several days to achieve correction Hard for patients to remain compliant
Demeclocycline	Effective in raising serum sodium	Slow response Potentially nephrotoxic Expensive
Loop diuretics with or without salt supplementation	May allow relaxation of fluid restriction and decreases urine-concentrating ability	Requires careful titration and monitoring Risk for other electrolyte abnormalities
Urea	Effective and inexpensive	Palatability Limited availability
Hypertonic (3%) saline	Effective for severe acute and symptomatic chronic hyponatremia	Risk of overly rapid correction Requires careful, intensive monitoring
Vasopressin receptor antagonists	Targets excessive arginine vasopressin Safe and effective Predictable rise in sodium values No risk for concomitant electrolyte disorders	Expensive Induces polyuria Requires close monitoring of serum sodium at initiation with inpatient admission

Table 2 | Key characteristics and outcomes of LIBRA and HARMONY

	LIBRA[7]		HARMONY[8]	
	Placebo	Lixivaptan	Placebo	Lixivaptan
No. of subjects	52	54	52	154
Mean age (years)	65.2	66.4	62.7	66.6
% on fluid restriction at baseline	65.4	37	11.5	16.9
Dose at initiation	None	50 mg (inpatient)	None	25 mg (outpatient)
Mean baseline sodium (mmol/l)	126.1	127.6	131.6	131.5
Increase in sodium at day 7 (mmol/l)	6.7 ± 0.7	4.5 ± 0.8	0.8 ± 0.6	3.2 ± 0.5
% of subjects with normalized sodium at day 7	23.1	44.4	12.2	39.4

requires careful laboratory monitoring and the ability to obtain rapid outpatient measurements of serum sodium values in order to assess for overly rapid correction of the serum sodium. At this time, such a strategy cannot be broadly recommended and requires further study to ensure safety.

Also unique to both the LIBRA and HARMONY trials was the inclusion of patients with symptoms believed to be attributable to hyponatremia (headache, fatigue, nausea, vomiting, irritability, mental slowing and confusion). However, these symptoms were not well defined, and unfortunately, there were no assessments as to whether these symptoms improved coincidently with correction of the hyponatremia. This was a missed opportunity, as prior trials with vaptans excluded such patients, and the indications for vaptan use in clinical practice are still uncertain. However, in both trials, in the lixivaptan treatment groups there were statistically significant improvements in the time required to complete the Trail Making Test part B (a neuropsychological test of visual attention and task switching), which were not seen in the placebo groups and are presumably attributable to improvement in the serum sodium levels. However, correlation of the improvement on this neuropsychological test with clinically meaningful improvement in hyponatremia-related symptoms cannot be assumed.

In both trials, the increases in serum sodium were modest, and the details regarding fluid restriction were at the discretion of the treating physician and not prescribed by the protocol. Furthermore, in the LIBRA trial there was a large imbalance in the percentage of patients who were on fluid restriction at baseline (65.4% in the placebo versus 37% in the lixivaptan group). This may suggest that the patients in the lixivaptan group had lower baseline urine osmolalities and tolerated higher daily water intakes, a factor that could confound the results of the study. Also of concern is that 33% of patients in the LIBRA cohort and 46.3% of patients in the HARMONY cohort were taking medications associated with hyponatremia. Many of these patients might have had restoration of normonatremia with simple cessation of the offending medication and would not have required therapy unless the medication was deemed indispensable.

Where does this leave us? Clearly vaptan drugs are effective in antagonizing the hydroosmotic effects of vasopressin and lead to a predictable rise in serum sodium levels in patients with euvolemic or hypervolemic hyponatremia. Lixivaptan (pending regulatory approval) now joins tolvaptan and conivaptan in this group of drugs. However, as others have pointed out, there is a large knowledge gap regarding key clinical questions that would inform us on how best to use these agents.[9] Most importantly, the indications for vaptans in the treatment of chronic hyponatremia remain uncertain. For instance: What symptoms associated with hyponatremia are indications for therapy? Is there an absolute level of hyponatremia that warrants therapy? What are the potential health-care-system cost savings associated with therapy of hyponatremia? Can treatment of hyponatremia impact the morbidity and mortality that have been associated with this laboratory abnormality? Thus far, clinical trials have not answered these key questions. Furthermore, patients with euvolemic hyponatremia differ greatly from those with hypervolemic hyponatremia, and in the hypervolemic group, patients with heart failure differ from those with cirrhosis. How do we tailor vaptan therapy for these groups? As an example,

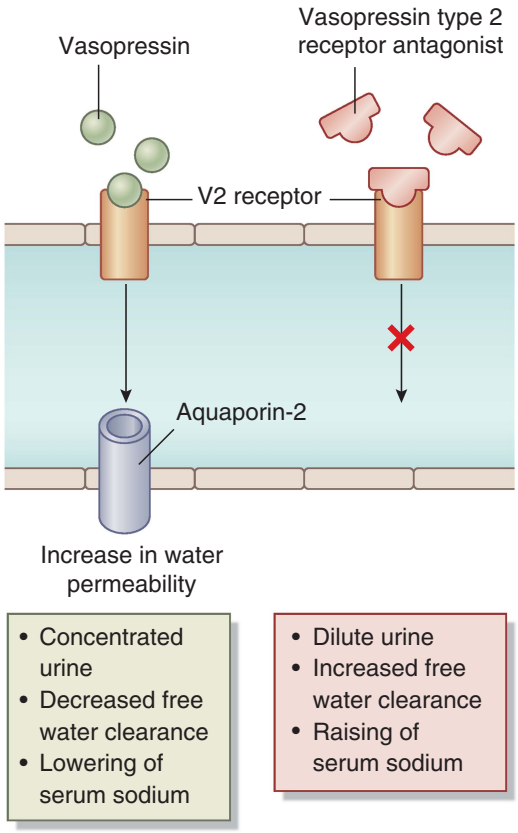

Figure 1 | Mechanism of action for vasopressin and V2-receptor antagonists. The binding of arginine vasopressin to the vasopressin V2 receptor (V2R) stimulates a G_s-coupled protein that activates adenylyl cyclase, in turn causing production of cyclic adenosine monophosphate to activate protein kinase A. This pathway increases the exocytosis of vesicles containing aquaporin water channels and inhibits endocytosis of the vesicles, both of which result in increases in aquaporin-2 channel formation and apical membrane insertion. This allows an increase in the permeability of water from the collecting duct. Vasopressin V2 receptors block this effect, and thus the collecting duct remains impermeable to water and free water excretion increases.

a recent trial of a vaptan drug in cirrhotics demonstrated a significant decrease in the number of paracenteses when a vaptan was added to usual care.[10] How do we think about these potential additive benefits of these drugs?

Clearly, the field of hyponatremia has advanced with the introduction of safe, effective drugs that antagonize the hydroosmotic effects of vasopressin. The two trials presented in this issue[7,8] add to the demonstrated benefits of vaptans to reliably increase serum sodium values. In recent years, the field has also seen a greater understanding of the association of hyponatremia with poor outcomes. However, prospective clinical trials need to go to the next step by investigating the appropriate indications for these drugs. Such trials would be the next logical step toward allowing clinicians to effectively treat hyponatremia and impact the morbidity and mortality associated with this common electrolyte disorder.

DISCLOSURE
The author declared no competing interests.

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